effective to trigger electrochemiluminescence in said plurality of cells, and

(c) photon detector means for detecting electrochemiluminescence from said sample.

REMARKS

Preliminary Matters

Applicant takes this opportunity to thank the Examiner for the courtesies extended to applicant's co-workers Dr. Sigal and Dr. Wilbur, and to applicant's representatives Mr. Evans and Mr. Rubin, during the December 12, 1997 personal interview of this application. This Amendment seeks to incorporate and place on the record the various understandings reached between applicant and the Examiner during the December 12 interview.

35 U.S.C. §102 and §103

Claims 1-39, 42-49, 61-65, 78 and 79 are rejected under 35 U.S.C. section §102 as allegedly being anticipated by, or under 35 U.S.C. section §103 as allegedly obvious over, United States Patent No. 5,240,863 to Shibue et al. ("Shibue").

Claims 1-39, 42-49, 61-65, 78 and 79 are rejected under 35 U.S.C. section §102 as allegedly being anticipated by, or under 35 U.S.C. section §103 as allegedly obvious over, United States Patent No. 5,093,268 to Leventis et al. ("Leventis").

For the reasons outlined below, applicant traverses these rejections.

The claimed invention is not anticipated by Shibue

The Examiner states that Shibue teaches detection of an immunoreactant in a sample by contacting that immunoreactant with ECL-labelled complementary immunoreactants immobilized on nanoparticles. The Examiner contends that this teaching reads on the expression "domains supported on a carrier" (Official Action, sentence bridging pages 3 and 4).

Applicant is somewhat confused by the Examiner's premise that Shibue's nanoparticle-immobilized immunoreactant reads on "domains supported on a carrier". The present invention *does not claim* "domains supported on a carrier." Shibue's nanoparticle-immobilized immunoreactant cannot "read on" what is not claimed.

Although Applicant is unsure of the precise claim or claim language alleged to be anticipated, the following comments seek to explain differences between what is presently claimed and what is disclosed in Shibue.

The present invention relates, in part, to ECL devices comprising binding reagents immobilized directly on an electrode support. The present invention also relates to ECL devices comprising *multiple* binding domains - each such domain being a

discreet physical region comprising immobilized binding reagents (which may be the same as or different from the binding reagents on other domains) - on a support. As described in the specification and in our previous submission, and as explained by Dr. Sigal at the December 12 personal interview, the discreet binding domains make virtually simultaneous ECL measurements possible since a separate electrochemiluminesence assay takes place at each binding domain. Using the devices of the invention, the electrochemiluminescence readings from particular binding domains can be quickly identified and analyzed, e.g., by imaging (as in claims 26-29) or using a plurality of addressible electrodes (as in claims 54, 66, 69 and 72).

The Examiner's attention is directed to Figure 4 of the attached appendix, entitled "Multi-Array Multi-Specific ECL Testing", which summarizes certain of the embodiments of the present invention.

Shibue employs a nanoscale-sized particle approximately 150-500 angstroms in diameter comprising a chemically and biologically inert core. The particle is coated with a biological material comprising an immunoreactant selected to be complementary to a particular analyte of interest. An electrochemiluminescent label substance is bound to the coating material. The particles are contacted with a sample possibly

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containing an analyte of interest, thereby forming a reaction mixture. After any present analyte is permitted to bind with its complement on the particle, an electrical current is imposed on the reaction mixture and electrochemiluminescence is measured.

A concise graphic summary of the Shibue invention is found in the schematic diagram in Figure 6b of the appendix to this amendment.

Specifically, regarding the §102 rejection, Shibue fails to disclose the claimed electrode-surface-immobilized binding reagents, the claimed plurality of discreet binding domains, the claimed discreet binding domains "having a relative spatial organization with respect to one another", and other specifically claimed features. The Examiner admits as much in stating that the references "differ from the instant claims in as much as they do not disclose an apparatus, system, article. . . or a kit as called for in the instant claims".

The carrier nanoparticles taught by Shibue are fundamentally different from, and cannot anticipate, the apparatus, articles, kits, methods and systems of the present invention. In view of the failure of Shibue to disclose essential claimed features, as noted by the Examiner, applicant requests reconsideration and withdrawal of the §102 rejection based on Shibue.

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The claimed invention is not rendered obvious by Shibue.

The claimed inventions are likewise not rendered obvious by Shibue. The respective operabilities of Shibue and the present inventions are fundamentally different.

--Binding Reagents Immobilized on Electrodes.

Shibue does not disclose ECL devices employing binding reagents immobilized directly on an electrode. Shibue employs clean electrodes - the electrochemiluminscent substances (hereinafter "TAG") of Shibue being immobilized on particles. For ECL to occur from a TAG molecule, the TAG molecule must typically be close enough to an electrode so that electron transfer between the TAG and the electrode can occur (a typical ECL reaction mechanism is described in Figure 2 of the appendix).

In Shibue, ECL occurs when particles labeled with TAG hit (by random diffusion) the electrode surface. Because the TAG is exposed on the surface of the particle, the distance between the TAG and the electrode is small and electron transport is efficient.

There are considerable advantages to having binding reagents immobilized on an electrode (as in the present invention) as opposed to requiring the diffusion of particles or reagents to the electrode surface (as in Shibue). A particular advantage is the ability to localize reagents in discrete binding

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domains in defined regions of the electrode. That binding reagents immobilized on an electrode would be useful in ECL assays, however, was not obvious from the experience of the prior art (for example, Shibue or assays using magnetic beads as diagrammed in Figure 4 of the appendix) for the reasons described below.

Figure 5 of the appendix compares schematically ECL excitation in assays using beads to ECL excitation in assays using binding reagents immobilized on an electrode. As diagrammed in Figure 5, in the excitation of ECL during bead-based assays the TAG is accessible to a clean electrode surface (i.e., distance "d" is small).

In contrast, in assays using binding reagents immobilized on an electrode, the organic layer formed on the electrode from the binding reagents and/or analyte would be expected to contribute to a considerably greater distance "d" between the TAG and the electrode (compared to the bead-based assay). Since the rate of electron transfer reactions decrease sharply with distance, the accepted thinking in the art was that an electrochemiluminescent substance must be very close to the electrode before ECL can be induced. Despite the presence of a thick organic layer on the electrodes, we have found,

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unexpectedly, that we get efficient ECL from TAG-labeled molecules bound to binding reagents immobilized on electrodes.

--Plurality of Binding Domains on a Support.

Shibue does not disclose a plurality of binding domains on a support. Shibue immobilizes binding reagents on particles that are freely suspended in solution. In contrast, the present invention relates in part to the binding reagents immobilized on a support (preferably an electrode) so as to form a plurality of binding domains. Multiple binding domains are created, each binding domain having reagent(s) specific for a particular analyte, and a plurality of different analytes in a sample may be determined simultaneously. Because binding domains are formed on defined areas of a support, it is possible to use simple approaches such as imaging to identify the ECL being emitted from a particular domain comprising a particular binding reagent complementary to a particular analyte. (Of course, the multi-array, multi-specific system is adaptable to certain alternate embodiments, including embodiments incorporating multiple electrodes triggered sequentially, embodiments where the support is not itself an electrode but rather is placed in contact with an electrode, and embodiments where more than one or all binding domains test for the same analyte.) The multi-array, multi-

specific concept is graphically described in detail in Figure 4 of the appendix.

Shibue does not teach or suggest multiple binding domains, multiple binding reagents or virtually simultaneous measurement. It is difficult to imagine how any of these features can be accomplished using methods, such as those of Shibue, that involve the random diffusion of particles from suspension to an electrode. Therefore, Shibue cannot render the claims of the present invention obvious.

In view of the above discussion, reconsideration and withdrawal of the §103 rejections of the pending claims based on Shibue is requested.

The claimed invention is not anticipated by Leventis

The Examiner argues that Leventis teaches an apparatus for conducting two or more simultaneous measurements of the ECL phenomena wherein two or more light detectors receive the emitted light at respective wavelengths of analytes of interest in the sample, and that Leventis therefore teaches an apparatus for conducting a plurality of measurements of the ECL phenomena. Applicant submits that merely because Leventis teaches a form of simultaneous measurement, it does not logically follow that Leventis is at all similar in operation to the claimed invention.

In fact, the present invention is nothing like this Leventis invention.

Leventis employs a *plurality of different types of ECL labels*, each label type capable of being induced to electrochemiluminescence *at a different wavelength*, and each label type linked to a substance complementary to a different analyte of interest. Different analytes are measured by detecting the luminescence at particular wavelengths by using a plurality of luminescence detection devices, each device calibrated to detect luminescence at a wavelength characteristic of a particular label. The number of analytes that can be detected simultaneously is limited to the number of available and spectrally distinguishable ECL labels. The Examiner is directed to Figure 6a of the appendix for a graphic explanation of the invention of Leventis.

In contrast to the method of Leventis, the methods of the present invention *do not* require the use of multiple types of ECL labels (hereinafter "TAGs"). The present invention employs a plurality of binding domains on a support. Each binding domain is the site of a discrete chemical interaction that can individually be subjected to assay techniques, including ECL techniques which result in assay results unique to that domain. Discrimination between different analytes, simultaneously or

otherwise, is achieved by the examination of assay results of particular binding domains, not by differences in wavelengths emitted from different ECL TAGs. Clearly, then, despite the fact that the practice of both Leventis and the present invention may result in obtaining multiple assay measurements, the measurements are obtained in ways that are fundamentally different from one another.

These limitations of Leventis are not present in the present invention since there is no need for labels capable of luminescing at different wavelengths.

More importantly, the limitations of the instant invention relating to the use of binding domains on a electrode surface, multiple binding domains, spatial orientation of binding domains and other limitations are not disclosed in Leventis.

In view of the failure of Leventis to disclose what is claimed, reconsideration and withdrawal of the §102 rejection based on this reference is requested.

The claimed invention is not rendered obvious by Leventis.

It is also clear that the Leventis invention does not render the present invention obvious. As described above, and as explained in the December 12 personal interview, despite Leventis and the present invention each being capable of simultaneous electrochemiluminescence assays, the respective inventions go

about accomplishing this result in completely different ways. There is no teaching of specific binding reagents immobilized on an electrode surface, "arrays" of multiple binding domains or spatial orientation of binding domains in Leventis. Leventis' invention, in fact, assumes that the variously functionalized particles are not to be separated according to type of binding reagent since this type of separation would eliminate the need for electrochemiluminescence TAGs which emit difficult wavelengths.

In view of these profound differences between Leventis and the present invention, it is urged that Leventis cannot render the present invention obvious. Reconsideration and withdrawal of the §103 rejection of the instance claims based on Leventis is therefore respectfully requested.

* * *

In view of the foregoing remarks, it is urged that the present application is in condition for allowance. Favorable

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reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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